46. (Amended) The nucleic acid molecule of claim 44 wherein said sequence encodes the contiguous amino acid sequence of SEQ ID NO:5.

II. REMARKS

Claims 1-12 and 44-55 are presently pending in this application.

Claims 1-12 and 44-45 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for reciting 90% identity, using the term "SEQ ID NO:2" and for referring to figures 4A-4C.

Claims 1-12, 44, 46, 49, 52 and 55 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly incorporating new matter.

Claims 1-12 and 44-55 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly not being enabled.

The specification was objected to for allegedly improper use of tradmarks, and for not disclosing the new address of ATCC.

The applicants acknowledge with appreciation the withdrawal of the rejections under 35 U.S.C. §§101, 102, and 103(a). These rejections are believed to be overcome by the above amendments and are otherwise traversed for reasons discussed below.

Overview of the Above Amendments

The specification was amended at page 18, lines 26-28, to identity the amino acid residues 29 through 256 as SEQ ID NO:5. In addition, the specification was amended to conform the use of the trademarks EMULSIGEN PLUS, TWEEN-80 and TWEEN-20 to the accepted practice, and to update the address of ATCC. The amendment finds support in the application as originally filed.

Claim 1-6 and 44-46 have been amended to delete reference to the Figures. In

No new matter has been added by way of these amendments. Further, the amendments are made solely to expedite prosecution, for reasons unrelated to patentability, and do not constitute an acknowledgment that the Examiners position is correct. In view of the foregoing amendments and following remarks, applicants submit that the claims are in condition for allowance.

Rejection Under 35 U.S.C. §112, Second Paragraph:

Claims 1-12 and 44-45 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for reciting 90% identity to amino acid of SEQ ID NO:2. The Examiner stated that there was no structural criteria, therefore, the identity of the nucleic acid was indefinite.

Applicants traverse the rejection. Under 35 U.S.C. §112, second paragraph, absolute specificity and precision are not required in the claims. Claims need only reasonably apprise a person having ordinary skill in the art as to their scope. *Hybritech Inc., v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, Fed. Cir. 1986. A claim which is clear to one ordinarily skilled in the art when read in light of the specification, does not fail for indefiniteness. *Allan Archery, Inc. v. Browning Manufacturing Co.*, 819 F.2d 1087, 2 USPQ2d 1490 (Fed. Cir. 1987).

The specification provides the techniques for determining the amino acid sequence identity on page 16, lines 1-31. The applicants' invention is directed towards nucleic acid molecules that encode immunogenic polypeptides having 90% sequence identity to SEQ ID NO:2 or 90% sequence identity to SEQ ID NO:5. In this context, the use of "90%" is conventional thereby conveying to one of ordinary skill in the art the metes and bounds of the present claim language. Therefore, the Examiner is respectfully requested to withdraw the rejection.

Claims 1-12 and 44-45 are rejected under 35 U.S.C. § 112, second paragraph, as

1 through 256 of SEQ ID NO:2 is now claimed as SEQ ID NO:2, and the amino acid sequence at positions 29 through 256 of SEQ ID NO:2 is now claimed as SEQ ID NO:5, and the reference to the Figures in the claims has been deleted. Therefore, the Examiner is respectfully requested to withdraw the rejection.

Rejection Under 35 U.S.C. §112, First Paragraph:

Claims 1-12 and 44-45 were rejected under 35 U.S.C. § 112, second paragraph, based on written description. The Examiner stated that "[n]owhere in the specification or drawings is there data teaching an isolated amino acid reciting the positions 29-256 with at least 90% identity."

The applicants traverse. The applicants have taught the amino acid sequence shown at positions 1 through 256 or SEQ ID NO:2. The specification further teaches on page 18, lines 27-29: "The mature *S. uberis* CAMP factor thus includes amino acid residues 29 through 256, inclusive, as depicted in Figures 4A-4C," and on page 16, lines 16-22 states: "Two DNA, or two polypeptide sequences are "substantially homologous" to each other when at least about 80%, preferably at least about 90%, and most preferably at least about 95% of the nucleotides or amino acids match over a defined length of the molecules, as determined using the methods above." In addition, the claims as filed, such as claim 3 for example, provides support for a homologus sequence to the amino acid sequence shown at positions 29 through 256 of SEQ ID NO:2. Thus, support for the recitation is provided by the specification, and the claims do not incorporate new matter. The Examiner is respectfully requested to withdraw the rejection.

Claims 1-12 and 44-55 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly not being enabled. The Examiner alleges that the specification does not provide guidance on which nucleic acids could be changed without causing a detrimental effect to the polypeptide. The Examiner cites Creighton, 1989 to teach that site directed

effect is difficult to know. The Examiner further cites Nosh *et al.* (1991) as teaching that a generalized mechanism for protein stability was not known. The Examiner than states that "it is unpredictable as to which nucleotides could be removed and which could be added" without causing a detrimental effect to the polypeptide produced, and "[i]t is unclear that a polypeptide could be produced from the nucleotide segments drawn to less than the full-length protein. Selective point mutation to one key antigen residue could, in practical terms, eliminate the ability of an antibody to recognize this altered antigen." The Examiner then concludes: "No working examples are shown containing the missing information. Without such information, one of skill in the art could not predict which deletions, substitutions or insertions or combination thereof would result in the desired polypeptide" and therefore could not make and/or use the invention without unde experimentation.

The applicants traverse. The test for enablement that the Examiner appears to be using is reasonable expectation of success criterion since the Examiner states one could not **predict** which positions could be substituted without a deleterious effect on the protein. The Examiner has applied an incorrect standard in rejecting the claims. The test for enablement is not the ability to predict a successful outcome before performing an experiment. Rather, the test for enablement is "whether one skilled in the art could make or use the claimed invention from the disclosure in the patent coupled with information known in the art without undue experimentation." United States v Teletronics, Inc. 8 USPQ2d 1217 (Fed. Cir. 1988); In re Wands, 8 USPQ2d 1400 (Fed Cir. 1988) (emphasis added). Thus, in order to satisfy Section 112 regarding enablement, the specification need only set forth such information as is sufficient to allow one of ordinary skill in the art to make and use the invention. How such a teaching is accomplished, either by the use of illustrative examples or by broad terminology, is of no importance since a

therein for enabling support (*In re Marzocchi*, 169 USPQ 367 (CCPA 1971)). The Office has failed to provide adequate evidence to support the present rejection. Without such evidence, a rejection under 35 U.S.C. §112, first paragraph for lack of enablement cannot be sustained.

The Examiner acknowledges that the applicants teach how to make substitutions, additions or deletions to sequences, but states that there is no reasonable expectation of success that such modifications would result in an antigen that is recognizable by an antibody. The applicants' invention is directed towards nucleic acid molecules that encode immunogenic polypeptides having 90% sequence identity to SEQ ID NO:2 or 90% sequence identity to SEQ ID NO:5. The applicants have provided the actual sequences of SEQ ID NO:2 and of SEQ ID NO:5, methods for determining homology to the sequences and methods for mapping epitopes contained within the immunogenic polypeptides (page 13, lines 10-20). In addition, in Example 6, the applicants carried out the process and demonstrated immunogenicity of the polypeptide. Thus, throughout their application, the applicants have provided considerable direction and guidance on how to practice their invention, and present working examples. With the sequences disclosed, and the methods needed to practice the invention either disclosed by the applicants or well known in the art, one of skill in the art could identify the claimed immunogenic polypeptides using routine experimentation. The application thus meets the test for enablement.

Predictable or reasonable expectation of success is not a test for enablement. The nature of antigen/antibody technology is such that it involves screening a large number of possible candidates in order to determine one with the desired characteristics. In the present case, the screening required is of routing nature, and therefore does not constitute undue experimentation.

required to teach how to make and use the invention that bears a reasonable correlation to the entire scope of the claims in order to satisfy the enablement requirement. *In re Fisher* 166 USPQ 18, 24 (CCPA 1970). The applicants have complied with the requirement.

The Examiner has not alleged that one of skill in the art could not carry out the invention without undue experimentation. Instead, the Examiner alleges that one of skill in the art could not predict beforehand which substitutions/additions/deletions would be undesirable. This is not the test for enablement. Using the methods described by the applicants, routine screening methods known in the art, one of skill in the art could identify the claimed immunogenic polypeptides without undue experimentation.

The Examiner cites a book published in 1989 and an article published in 1991 to support the proposition that the effect of point mutations on protein stability cannot be predicted. However, the Examiner does not characterize these publications as stating that undue experimentation would be required to determine whether or not the protein product was stable and/or had the desired biological activity. As stated above, routine screening assays could be performed to determine if the polypeptide obtained was immunogenic.

It is well-established and accepted by the scientific community that a particular degree of percentage identity over a particular length of a protein is sufficient to establish a likelihood of homology and shared functionality. Applicants respectfully draw the Examiner's attention to the attached paper by Steven Brenner *et al.* (1998) *Proc. Natl. Acad. Sci. USA* 95:6073-6078. Through exhaustive analysis of a dataset of proteins with known structural and functional relationships, Brenner *et al.* have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues, and that 40% identity is a reliable threshold when aligned over at least 70 residues (pages 6073 and 6076).

A reading of Brenner *et al.* will reveal that the authors analyzed many individual

unrelated proteins will show a certain percentage identity to each other over a certain length?" i.e., 50% identity over 150 residues. In this way, *Brenner et al.* evaluated the reliability of using sequence comparison methods to determine the evolutionary and functional relationships between pairs of proteins. In order to conduct an analysis that was not wholly tautologous (i.e. because the degree of relatedness had been previously determined by sequence comparisons), the authors needed to select proteins whose structure and function were already well defined, and had been determined by methods other than sequence comparison. That is why the authors used the PDB, a database with over 12,000 molecules with structures and functions identified by methods other than sequence comparison.

As a result of their analysis, Brenner *et al.* produced a graph (Fig. 3) that clearly shows the probability of two unrelated proteins sharing a certain degree of sequence identity over a certain length. One of skill in the art would not expect the results reported in the Brenner *et al.* paper to be specific to the data analyzed in that paper, but would expect them to be generally applicable to proteins compared using standard sequence comparison methods (Brenner et al., 6074, col.2, last sentence of para. 4). Additionally, Brenner *et al.* further state with regard to pairwise sequence comparison methods such as BLAST that: "Because many homologs have low sequence similarity, most distant relationships cannot be detected by any pairwise comparison method; however *those which are identified may be used with confidence*". (Emphasis added.).

As reported in the specification SEQ ID NO: 2 has 256 amino acids and SEQ ID NO:5 has 227 amino acids. A sequence having at least 90% sequence identity to the contiguous amino acid sequences of SEQ ID Nos: 2 or 5 well exceedes the statistical threshold required for reliable prediction of homology. Considering the above evidence and reasoning, applicants assert that one of ordinary skill in the art would reasonably

The applicants submit that they have complied with the enablement requirement of 35 U.S.C. § 112, first paragraph. The Examiner is therefore respectfully requested to withdraw the rejection.

Objections

The specification was objected to for not using the new address of ATCC and for the non-acceptable use of the trademark. The applicants have amended the specification as suggested by the Examiner.

III. CONCLUSION

Applicants respectfully submit that the claims are novel and nonobvious over the art and comply with the requirements of 35 U.S.C. §112. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated.

If the Examiner notes any further matters which he believes may be expedited by a telephone interview, he is requested to contact the undersigned attorney at (650) 325-7812.

Respectfully submitted,

Date: _____ By: _____

Narinder S. Banait
Registration No. 43,482

ROBINS & PASTERNAK LLP
545 Middlefield Road, Suite 180
Menlo Park, CA 94025
Telephone: (650) 325-7812

APPENDIX A

Marked-up Version

The specification, at page 18, lines 20-35, was amended as follows:

As shown in Figures 4A-4C, the *S. uberis* CAMP factor gene encodes a preprotein of about 256 amino acids (amino acid residues 1 through 256, inclusive, of Figures 4A-4C) that includes an N-terminal signal sequence approximately 28 amino acids in length. The precursor molecule has a calculated molecular weight of 28,363 Da. The mature *S. uberis* CAMP factor thus includes amino acid residues 29 through 256 --(SEQ ID NO:5)--, inclusive, as depicted in Figures 4A-4C. As discussed further below, the portion of the CAMP factor gene encoding the signal sequence can be included in constructs that encode the CAMP factor to direct secretion of the CAMP factor upon expression. Additionally, the CAMP factor signal sequence and the nucleic acid sequence encoding the same can be used with heterologous proteins and nucleic acid molecules, to aid in the secretion thereof.

The specification at page 34, lines 18-31, was amended as follows:

A deposit of biologically pure cultures of the following strains was made with the American Type Culture Collection, --10801 University Boulevard, Manassas, VA 20110-2209-- [12301 Parklawn Drive, Rockville, Maryland], under the provisions of the Budapest Treaty. The accession number indicated was assigned after successful viability testing, and the requisite fees were paid. The designated deposits will be maintained for a period of thirty (30) years from the date of deposit, or for five (5) years after the last request for the deposit, whichever is longer. Should a culture become nonviable or be inadvertently destroyed, or, in the case of plasmid-containing strains, lose its plasmid, it will be replaced with a viable culture(s) of the same taxonomic description

The specification at page 43, lines 20-29, was amended as follows:

S. uberis CAMP factor, encoded by pGH-CAMP, was prepared from inclusion bodies as described in Example 1. The antigen was formulated in VSA3 adjuvant which is a combination of [Emulsigen Plus™] --EMULSIGEN PLUS-- from MVP Laboratories, Ralston, Nebraska and Dimethyldioctadecyl ammonium bromide (DDA) from Kodak (Rochester, NY). The final concentration was 25 µg per ml of CAMP factor, 30% [Emulsigen Plus] --EMULSIGEN PLUS--, 0.9% [Tween-80] --TWEEN-80--, and 2.5 mg per ml of DDA. The dose volume was 2 cc containing 50 µg of recombinant antigen.

The specification at page 45, line 11 to page 46, line 2, was amended as follows:

Total Ig titers for CAMP factor were determined by an indirect ELISA. Immunlon-2 plates were coated with antigen in carbonate buffer. Prior to use, the plates were blocked with TBST (100 mM Tris Cl, pH 8.0; 150 mM NaCl; 0.05% [Tween-20] --TWEEN-20--) and 3% BSA for 1 hour. After blocking, the plates were washed with distilled water. Serum and milk samples were serially diluted in 3-fold increments using TBST containing 1% BSA. Rabbit antisera for *S. uberis* CAMP factor was also diluted and served as a positive control. Negative control samples contained TBST with 1% BSA. The diluted samples and controls were transferred to the coated plates and were incubated for 1 hour at room temperature. The plates were washed thoroughly with distilled water and all wells were incubated with a horse radish peroxidase conjugate of goat anti-IgG diluted 1:2000 in TBST containing 1% BSA. Following a 1 hour incubation at room temperature, the plates were washed with distilled water. The amount of antibody present in samples was visualized using ABT substrate. The titers of each sample were based on the absorbance reading at 405 nm with a reference wavelength of

reciprocal of the last dilution giving a positive reading. Consistency among assay plates was monitored by the absorbance reading of positive controls.

In the claims:

Claims 1-6 and 44-46 were amended as follows.

1. (Four times amended) An isolated nucleic acid molecule consisting of a sequence selected from the group consisting of: (a) a sequence encoding an immunogenic polypeptide having at least 90% sequence identity to the contiguous amino acid sequence shown at positions 1 through 256, inclusive, of [Figures 4A-4C (SEQ ID NO:2)] SEQ ID NO:2; and (b) a sequence encoding an immunogenic polypeptide having at least 90% sequence identity to the contiguous amino acid sequence shown at positions 29 through 256, inclusive, of [Figures 4A-4C (SEQ ID NO:2)] SEQ ID NO:5.

2. (Five times amended) The nucleic acid molecule of claim 1 wherein said nucleic acid molecule encodes an immunogenic polypeptide having a sequence with at least 90% sequence identity to the contiguous amino acid sequence shown at positions 1 through 256, inclusive, of [Figures 4A-4C (SEQ ID NO:2)] SEQ ID NO:2.

3. (Four times amended) The nucleic acid molecule of claim 1 wherein said nucleic acid molecule encodes an immunogenic polypeptide having a sequence with at least 90% sequence identity to the contiguous amino acid sequence shown at positions 29 through 256, inclusive, of [Figures 4A-4C (SEQ ID NO:2)] SEQ ID NO:5.

4. (Four times amended) A recombinant vector comprising:

[illegible]

256, inclusive, of [Figures 4A-4C (SEQ ID NO:2)] SEQ ID NO:2; and (ii) a sequence having at least 90% sequence identity to the contiguous amino acid sequence shown at positions 29 through 256, inclusive, of [Figures 4A-4C (SEQ ID NO:2)] SEQ ID NO:5; and

(b) control elements that are operably linked to said nucleic acid molecule whereby said coding sequence can be transcribed and translated in a host cell, and at least one of said control elements is heterologous to said coding sequence.

5. (Four times amended) A recombinant vector according to claim 4, wherein said nucleic acid molecule encodes an immunogenic polypeptide which comprises a sequence having at least 90% sequence identity to the contiguous amino acid sequence shown at positions 1 through 256, inclusive, of [Figures 4A-4C (SEQ ID NO:2)] SEQ ID NO:2.

6. (Four times amended) A recombinant vector according to claim 4, wherein said nucleic acid molecule encodes an immunogenic polypeptide which comprises a sequence having at least 90% sequence identity to the contiguous amino acid sequence shown at positions 29 through 256, inclusive, of [Figures 4A-4C (SEQ ID NO:2)] SEQ ID NO:5.

44. (Amended) An isolated nucleic acid molecule comprising a sequence selected from the group consisting of: (a) a sequence encoding the contiguous amino acid sequence shown at positions 1 through 256, inclusive, of [Figures 4A-4C (SEQ ID NO:2)] SEQ ID NO:2; and (b) a sequence encoding the contiguous amino acid sequence shown at positions 29 through 256, inclusive, of [Figures 4A-4C (SEQ ID NO:2)] SEQ ID NO:5.

45. (Amended) The nucleic acid molecule of claim 44 wherein said sequence

[illegible] SEQ ID NO:[illegible] SEQ ID NO:[illegible].

46. (Amended) The nucleic acid molecule of claim 44 wherein said sequence encodes the contiguous amino acid sequence shown at positions 29 through 256, inclusive, of [Figures 4A-4C (SEQ ID NO:2)] SEQ ID NO:5.